

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202293Orig1s000

CHEMISTRY REVIEW(S)

Farxiga (dapagliflozin) Tablets 5 and 10 mg

NDA 202293

Chemistry, Manufacturing, and Controls Division Director's Summary Basis of Action

Applicant: Bristol-Meyers Squibb Co
Wallingford CT

Reviewers: Xavier Ysern
Muthukar Ramaswamy

Pharmacological Category:

Dapagliflozin is an orally active sodium glucose co-transporter 2 (SGLT-2) inhibitor, proposed for the treatment of type 2 diabetes mellitus

Presentations:

The drug product, Farxiga (dapagliflozin) Tablets, is formulated as immediate release film-coated tablets. Two dose strengths are proposed for marketing, 5 and 10 mg, to be supplied in 95-cc (30-count) and 200-cc (90-count) HDPE bottles (b) (4) and in (b) (4) blister. (b) (4)

Consults:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	30-Oct-2013	A. Inyard
Pharm/Tox	--		
Biopharm	Approval	27-May-2011	Dr. Minerva Hughes
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories is not recommended		
DMEPA	Farxiga proprietary name accepted as tradename	07-Oct-2013	Carol Holquist, RPh
EA	Acceptable		Part of this review
Microbiology	APPROVE - See Microbiology Review	31-Aug-2011	Dr. Steve Fang

DMEPA = Division of Medication Error Prevention and Analysis.

Drug Substance:

The DS will be manufactured at the BMS facility in Swords, Ireland (b) (4)

(b) (4)

(b) (4)

Drug substance specifications include appearance, color, identification (IR or Raman, and HPLC), assay (dapagliflozin content by HPLC), (b) (4) content, water content, residual solvents (b) (4) purity (b) (4). All these specifications were identified by the Applicant as critical quality attributes established for the drug substance linked to patient safety. (b) (4) Available release data from 30 batches showed that the highest value observed (b) (4) is (b) (4) and for 24 of these batches its value was (b) (4) (reporting limit)

Retest period (b) (4) is supported by submitted stability data.

Drug Substance: Satisfactory

Drug Product:

The Applicant used Quality by Design (QbD) approach to develop the proposed drug product manufacturing process. Quality target product profile (QTPP) is defined.

The formulations contain dapagliflozin (active moiety), anhydrous lactose (b) (4) microcrystalline cellulose (b) (4) silicon dioxide (b) (4), crospovidone (b) (4), magnesium stearate (b) (4) and (b) (4). All excipients, including the components of the coating agent, meet compendial requirements. The two strengths are differentiated by debossed markings, shape and size. The formulations contain dapagliflozin (active moiety), anhydrous lactose (b) (4) microcrystalline cellulose (b) (4) silicon dioxide (b) (4), crospovidone (b) (4), magnesium stearate (b) (4), and (b) (4).

Drug product specifications include appearance or description (visual examination), identification (IR and HPLC), assay (HPLC), impurities (HPLC), disintegration as surrogate of dissolution, content uniformity and (b) (4). Regarding impurities, acceptance criteria requires (b) (4) (u) (+)

Of note - the applicant requested approval for the use of disintegration testing as a surrogate for dissolution for routine quality control - acceptable.

Expiry of 24 months is supported by data from 24 months which show little or no change for samples packaged in HDPE bottles or (b) (4) blisters.

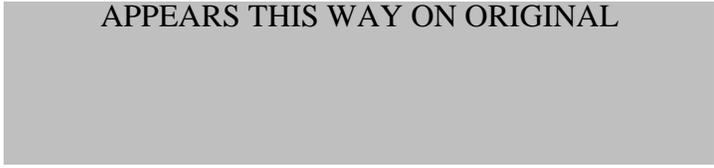
Labeling is acceptable.

Drug Product: Satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

APPEARS THIS WAY ON ORIGINAL



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/s/

ERIC P DUFFY
01/07/2014

NDA 202-293

Farxiga (dapagliflozin) Tablets 5 and 10 mg

Bristol-Myers Squibb (BMS) Company

Muthukumar Ramaswamy PhD

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

(Clinical Review Division: DMEP)

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Chemistry Review Data Sheet

1. NDA: 202-293
2. REVIEW #: 3
3. REVIEW DATE: 30-October-2013
4. REVIEWER(s): Muthukumar Ramaswamy, PhD, and Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

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Document Date

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6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
<i>Original</i>	<i>27-Dec-2010</i>
Amendment(s)	
0104	09-Sep-2013 (Farxiga proposed as proprietary)
0098	16-Jul-2013 (Forxiga proposed as proprietary)
0095	11-Jul-2013 (Resubmission; Agency's CR letter dated 17-Jan-2012)
0040	17-Aug-2011 (updated drug product specifications)
0034	24-Jun-2011 (response to information request on 15-Jun-2011)
0022	20-May-2011 (Stability Data Batches manufactured at the commercial site, Humacao, PR)
0008	23-Mar-2011 (Response to 4-Mar-2011 Filing Letter)
0005	31-Jan-2011 (Proprietary name and alternate proprietary name)
0002	05-Jan-2011 (Establishment and patent information)

7. NAME & ADDRESS OF APPLICANT:

Name: Bristol-Myers Squibb (BMS) Company
Address: 5 Research Parkway
Wallingford, CT 06492-7660
Representative: Amy A. Jennings, Ph.D.
Director, US /Global Regulatory Lead-Dapagliflozin
Bristol-Myers Squibb Company
Telephone: 203-677-3821 [fax 203-677-7435 email amy.jennings@bms.com]

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Farxiga (proprietary name proposed on 09-Sep-2013 and accepted as tradename on 07-Oct-2013). ["Forxiga", requested on 16-Jul-2013, was amendment to "Farxiga" on 09-Sep-2013.]
Initially (b) (4) was selected by Astra Zeneca and Bristol-Myers Squibb as the primary candidate for the proprietary name, (b) (4) selected as the secondary candidate (31-Jan-2011)
- b) Non-Proprietary Name (USAN): Dapagliflozin
- c) Code Name: BMS-512148
- d) Chem. Type/Submission Priority: · Chem. Type: 1 (new molecular entity)

· Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)
10. PHARMACOL. CATEGORY: Dapagliflozin is an orally active sodium glucose co-transporter 2 (SGLT-2) inhibitor, proposed for the treatment of type 2 diabetes mellitus.
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 5- and 10-mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. SPOTS (Special Products On-Line Tracking System): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

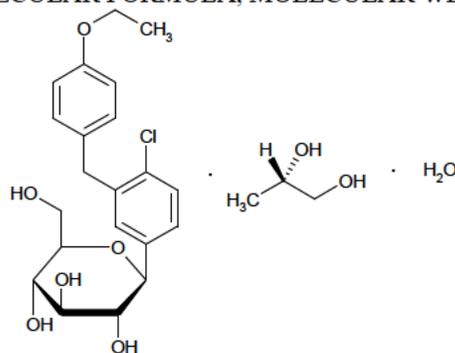
Dapagliflozin propanediol monohydrate

$C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$

MW: 502.98 (Dapagliflozin propanediol monohydrate)
408.87 (Dapagliflozin)

CAS registry #: 960404-48-2

Laboratory Code: BMS-512148-05



D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1)

(2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol,(2S)-propane-1,2-diol (1:1) monohydrate (IUPAC Name)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code ^a	Status ^b	LOA date	Comments
Type III		(b) (4)	4	Adequate	10-Aug-2010	DMF (b) (4) pp 1-52
			4	Adequate	12-Jan-2010	21 CFR§314.420
			4	Adequate	29-Jun-2010	(b) (4)
			4	Adequate	09-Sep-2010	21 CFR§210&211
Type IV		(b) (4)	4	Adequate	11-Nov-2010	DMF (b) (4) page 6399 Filed 16-Nov-2009

^a Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows: 2 -Type 1 DMF; 3- Reviewed previously and no revision since last review
4 – Sufficient information in application; 5 – Authority to reference not granted; 6 – DMF not available; 7 – Other (explain under "Comments")

^b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,652	BMS' Dapagliflozin (b) (4)

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable (EES Summary Report is attached)	30-Oct-2013	A. Inyard
Pharm/Tox	--		
Biopharm	Approval	27-May-2011	Dr. Minerva Hughes
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories is not recommended		
DMEPA	Farxiga proprietary name accepted as tradename	07-Oct-2013	Carol Holquist, RPh
EA	Acceptable		Part of this review
Microbiology	APPROVE - See Microbiology Review	31-Aug-2011	Dr. Steve Fang

DMEPA = Division of Medication Error Prevention and Analysis.

The Chemistry Review for NDA 202-293

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From CMC point of view this application is recommended for APPROVAL.

Based on the stability data submitted, an expiry of 24 months for drug product packaged in either HDPE bottles (b) (4) packaged in (b) (4) blisters is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

- Drug substance [Dapagliflozin]

The drug substance (DS), dapagliflozin propanediol monohydrate, is a (b) (4) 1:1:1 mixture of dapagliflozin, propanediol and water (designated as BMS-512148-05). Its chemical name is D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1), empirical formula $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$, and molecular weight 502.98 g/mol (Dapagliflozin 408.87). The active component, dapagliflozin, is a potent, highly selective and orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption, leading to urinary glucose excretion (glucuresis). The mode of action is independent of the presence of insulin.

Dapagliflozin propanediol monohydrate is a (b) (4) compound. Dapaglizin According to the Biopharmaceutics Classification System (BCS) the drug substance is a class 3 compound (low permeability, high solubility). (b) (4)

The DS will be manufactured at the BMS facility in Swords, Ireland (b) (4)

The Applicant has used quality by design principles to develop the drug substance manufacturing process. Risk assessment techniques were used to assess the influence of process parameters to impact the quality attributes of the intermediates and critical quality attributes of the drug substance. There are no critical process parameters associated with the drug substance manufacturing process. The applicant has identified and defined control ranges for key process parameters (proven acceptable ranges). In addition, the application contains adequate specification for raw materials, intermediates and final drug substance.

Drug substance specifications include appearance, color, identification (IR or Raman, and HPLC), assay (dapagliflozin content by HPLC), (b)(4) content, water content, residual solvents (b)(4) purity (b)(4)

All these specifications were identified by the Applicant as critical quality attributes established for the drug substance linked to patient safety. (b)(4)

Available release data from 30 batches showed that the highest value observed (b)(4) is (b)(4) and for 24 of these batches its value was (b)(4) (reporting limit).

The available stability data drug substance, which includes (b)(4) storage at long-term conditions (25 °C/60 % RH) and also at 30 °C/65 % RH and 5 °C, 6 months at accelerated conditions (40 °C/ 75 % RH), and diverse stress conditions, showed that the drug substance is a stable compound under these conditions. The proposed re-test period (b)(4) under the recommended storage condition, (b)(4) is fully supported by the stability data.

Waiver granted: Removal of testing for (b)(4) content after successful manufacturing of release of first 10 batches.

- Drug Product [Farxiga (dapagliflozin) Tablets]

The drug product, Farxiga (dapagliflozin) Tablets, is formulated as immediate release film-coated tablets. Two dose strengths are proposed for marketing, 5 and 10 mg, to be supplied in 95-cc (30-count) and 200-cc (90-count) HDPE bottles (b)(4) and in (b)(4) blister. (b)(4)

The formulations contain dapagliflozin (active moiety), anhydrous lactose (b)(4), microcrystalline cellulose (b)(4), silicon dioxide (b)(4), crospovidone (b)(4), magnesium stearate (b)(4). All excipients, including the components of the coating agent, meet compendial requirements. The two strengths are differentiated by debossed markings, shape and size.

The Applicant used Quality by Design (QbD) approach to develop the proposed drug product manufacturing process. Quality target product profile (QTPP) is defined. The manufacturing process uses a (b)(4) process (b)(4)

The Firm has proposed a maximum batch size (b)(4) for the commercial manufacturing operation. The proposed manufacturing process consists of (b)(4) operation (b)(4)

The Applicant has completed a manufacturing process risk assessment using Failure Mode and Effect Analysis (FMEA) and assigned a high Risk priority number (RPN) (b)(4)

These steps are considered critical steps as they are linked to the following quality attributes: assay, content uniformity, appearance, dissolution and disintegration and the Firm has proposed limits for these critical process parameters.

The Applicant used experimental design approach (DOE) to establish a design space for the commercial process. The design space includes ranges for the process parameters and process attributed used to control respective unit operation.

Drug product specifications include appearance or description (visual examination), identification (IR and HPLC), assay (HPLC), impurities (HPLC), disintegration as surrogate of dissolution, content uniformity (b) (4). Regarding impurities, acceptance criteria requires (b) (4).

All drug product critical attributes identified by risk assessment and developmental studies are part of the specifications.

The Applicant has performed manufacture of a total of nine commercial scale batches (b) (4) to demonstrate the transferability of the manufacturing process.

Six batches (three 5 mg and three 10 mg strength batches) have been manufactured to conduct the primary stability study. The stability program consists of long term testing at 25 °C/60 % RH and 30 °C/65 % RH, accelerated testing at 40 °C/75 % RH. The stability protocol includes matrix testing design. The long term stability is still ongoing, but data from the first 24 months are available and show that little or no change was observed for samples packaged in HDPE bottles or (b) (4) blisters (proposed commercial packaging). The 6 month study under accelerated conditions has been completed and their results show that the drug product is stable when stored in HDPE bottles or (b) (4) blisters at 40 °C/75 % RH for up to six months. The requested expiry dating of 24 months for the drug product packaged into HDPE bottles (b) (4) or into (b) (4) blisters at the recommended storage condition: "Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86 °F), is fully supported by the provided stability data. (b) (4)

Waivers granted: (1) Disintegration testing as a surrogate for dissolution testing for release and shelf-life, and (2) No impurities/degradants testing for batch release.

B. Description of How the Drug Product is Intended to be Used

Farxiga Tablets are film-coated tablets designed for immediate release of dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Farxiga (dapagliflozin) Tablets, available in 10 mg, are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended dose of Farxiga is 10 mg taken once daily at anytime of the day regardless of meals. The efficacy of Farxiga is dependent on renal function. Farxiga should not be used in patients with moderate to severe renal impairment or for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

C. Basis for Approvability or Not-Approval Recommendation

The initial NDA was submitted on 28 December 2010, and FDA issued a Complete Response (CR) Letter on 17 January 2012 (no new CMC information was requested as part of the CR letter). Product safety concerns were the main reason for FDA's CR action (e.g., increased cancer risk, liver toxicity, and cardiovascular safety). An approval recommendation from the CMC viewpoint was given on 31-Oct-2011 (see CMC Review # 2). However, since more than 2 years have elapsed from the original submission, a new request for the evaluation of the facilities involved in the manufacture of the drug substance and drug product was requested, and an acceptable recommendation by the Office of Compliance was issued on 29-Oct-2013 (attached).

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf life. Quality by design (QbD) concepts have been used during development of both drug substance and drug product manufacture. All Applicant's requests, listed below, are deemed acceptable:

Drug Substance:

- Removal of testing for (b) (4) content after successful manufacturing of release of first 10 batches.

Drug Product:

- Disintegration testing as a surrogate for dissolution testing for release and shelf-life
- No impurities/degradants testing for batch release.

III. Administrative

A. Reviewer's Signature

Muthukumar Ramaswamy PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 30-Oct -2013

Xavier Ysem, PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 30-Oct-2013

B. Endorsement Block

Danae Christodoulou, PhD Acting Branch Chief/ONDQA/ DNDQA III/ Branch VII Date: 30-Oct-2013

C. CC Block

Mehreen Hai Project Manager, OND/ ODE II/ DMEP

Chemistry Assessment**I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data**

See CMC Reviews # 1 and # 2.

Attached:

EER Summary Report (30-Oct-2013, 2 pages)

Page
11



FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 202293.000 Sponsor: BRISTOL MYERS SQUIBB
Org. Code: 510 5 RESEARCH PKY
Priority: 1 WALLINGFORD, CT 06492
Stamp Date: 28-DEC-2010 Brand Name: DAPAGLIFLOZIN
PDUFA Date: 11-JAN-2014 Estab. Name:
Action Goal: Generic Name: DAPAGLIFLOZIN
District Goal: 12-NOV-2013 Product Number; Dosage Form; Ingredient; Strengths
002; TABLET; DAPAGLIFLOZIN; 10MG
001; TABLET; DAPAGLIFLOZIN; 5MG

FDA Contacts: S. HERTZ Facility Reviewer (HFD-320) 3017963203
X. YSERN Prod Qual Reviewer 3017961779
S. FONG Micro Reviewer (HFD-003) 3017961501
R. MCKNIGHT Product Quality PM 3017961765
A. ADEOLU Regulatory Project Mgr (HFD-400) 3017964264
S. TRAN Team Leader 3017961764

Overall Recommendation: ACCEPTABLE on 29-OCT-2013 by R. SAFAAI-JAZI 0 3017964463
PENDING on 17-JUL-2013 by EES_PROD
PENDING on 17-JUL-2013 by EES_PROD
ACCEPTABLE on 25-OCT-2011 by A. ALEXANDROW (HFD-001) 3017965363

Establishment: CFN: 2623468 FEI: 2623468
BRISTOL MYERS SQUIBB MANUFACTURING COMPANY

DMF No: HUMACAD, , UNITED STATES 00792 AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-AUG-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 1825662 FEI: 1825662
BRISTOL-MYERS SQUIBB COMPANY, INC.
MOUNT VERNON, , UNITED STATES 476209682 AADA:
DMF No:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: TABLETS, PROMPT RELEASE OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-OCT-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: (b) (4) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-JUL-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XAVIER J YSERN
10/31/2013

DANAE D CHRISTODOULOU
10/31/2013

I concur with the reviewer's conclusion and recommendations

NDA 202-293

 ^{(b) (4)} **(dapagliflozin) Tablets**
5 and 10 mg

Bristol-Myers Squibb (BMS) Company

Muthukumar Ramaswamy PhD

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

(Clinical Review Division: DMEP)

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III. Administrative	9
A. Reviewer's Signature	9
B. Endorsement Block	9
C. CC Block	9
Chemistry Assessment <i>{Referred to CMC Review # 1.}</i>	10
Attachments	11

Chemistry Review Data Sheet

- 1. NDA: 202-293
- 2. REVIEW #: 2
- 3. REVIEW DATE: 31-October-2011
- 4. REVIEWER(s): Muthukumar Ramaswamy, PhD, and Xavier Ysern, PhD
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

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6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed Document Date

Original	27-Dec-2011
Amendment(s):	
0040	17-Aug-2011 (updated drug product specifications)
0034	24-Jun-2011 (response to information request on 15-Jun-2011)
0022	20-May-2011 (Stability Data Batches manufactured at the commercial site, Humacao, PR)
0008	23-Mar-2011 (Response to 4-Mar-2011 Filing Letter)
0005	31-Jan-2011 (Proprietary name and alternate proprietary name)
0002	05-Jan-2011 (Establishment and patent information)

7. NAME & ADDRESS OF APPLICANT:

Name: Bristol-Myers Squibb (BMS) Company
 Address: 5 Research Parkway
 Wallingford, CT 06492-7660
 Representative: Amy A. Jennings, Ph.D.
 Director, US /Global Regulatory Lead-Dapagliflozin
 Bristol-Myers Squibb Company
 Telephone: 203-677-3821 [fax 203-677-7435 email amy.jennings@bms.com]

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b)(4) is selected by Astra Zeneca and Bristol-Myers Squibb as the primary candidate for the proprietary name, (b)(4) selected as the secondary candidate (31-Jan-2011)
 Division of Medication Error Prevention and Analysis (DMEPA) does not have objection to proposed proprietary name (b)(4) (04-Apr-2011)
- b) Non-Proprietary Name (USAN): Dapagliflozin
- c) Code Name: BMS-512148
- d) Chem. Type/Submission Priority:
 - Chem. Type: 4 (new combination)
 - Submission Priority: S (substantially equivalent)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Dapagliflozin is an orally active sodium glucose co-transporter 2 (SGLT-2) inhibitor, proposed for the treatment of type 2 diabetes mellitus.
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 5- and 10-mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

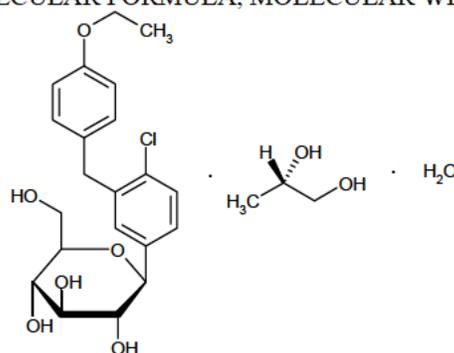
Dapagliflozin propanediol monohydrate

$C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$

MW: 502.98 (Dapagliflozin propanediol monohydrate)
408.87 (Dapagliflozin)

CAS registry #: 960404-48-2

Laboratory Code: BMS-512148-05



D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1)

(2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol,(2S)-propane-1,2-diol (1:1) monohydrate (IUPAC Name)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code ¹	Status ²	LOA date	Comments
Type III		(b) (4)	4	Adequate	10-Aug-2010	DMF (b) (4) pp 1-52
			4	Adequate	12-Jan-2010	21 CFR§314.420
			4	Adequate	29-Jun-2010	(b) (4)
			4	Adequate	09-Sep-2010	21 CFR§210&211
Type IV		(b) (4)	4	Adequate	11-Nov-2010	DMF (b) (4) page 6399 Filed 16-Nov-2009

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,652	BMS' Dapagliflozin (b) (4)

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable (EES Summary Report is attached)	25-Oct-2011	A. Inyard
Pharm/Tox	--		
Biopharm	Approval	27-May-2011	Dr. Minerva Hughes
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
DMEPA	No objection to the proposed Proprietary tradename (b) (4)	04-Apr-2011	
Methods Validation	Revalidation by Agency laboratories is not recommended		
OPDRA			
EA	Acceptable		Part of this review
Microbiology	APPROVE - See Microbiology Review	31-Aug-2011	Dr. Steve Fang

DMEPA = Division of Medication Error Prevention and Analysis.

The Chemistry Review for NDA 22-107

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From CMC point of view this application is recommended for APPROVAL.

Based on the stability data submitted, an expiry of 24 months for drug product packaged in either HDPE bottles (b) (4) packaged (b) (4) blisters is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

- Drug substance

The drug substance (DS), dapagliflozin propanediol monohydrate, is a (b) (4) 1:1:1 mixture of dapagliflozin, propanediol and water (designated as BMS-512148-05). Its chemical name is D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1), empirical formula $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$, and molecular weight 502.98 g/mol (Dapagliflozin 408.87). The active component, dapagliflozin, is a potent, highly selective and orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption, leading to urinary glucose excretion (glucuresis). The mode of action is independent of the presence of insulin.

Dapagliflozin propanediol monohydrate is a (b) (4) compound. Dapaglizin According to the Biopharmaceutics Classification System (BCS) the drug substance is a class 3 compound (low permeability, high solubility). (b) (4)

The DS will be manufactured at the BMS facility in Swords, Ireland (b) (4)

The Applicant has used quality by design principles to develop the drug substance manufacturing process. Risk assessment techniques were used to assess the influence of process parameters to impact the quality attributes of the intermediates and critical quality attributes of the drug substance. There are no critical process parameters associated with the drug substance manufacturing process. The applicant has identified and defined control ranges for key process parameters (proven acceptable ranges). In addition, the application contains adequate specification for raw materials, intermediates and final drug substance.

Drug substance specifications include appearance, color, identification (IR or Raman, and HPLC), assay (dapagliflozin content by HPLC), (b)(4) content, water content, residual solvents (b)(4) purity (b)(4)

All these specifications were identified by the Applicant as critical quality attributes established for the drug substance linked to patient safety. (b)(4)

Available release data from 30 batches showed that the highest value observed (b)(4) is (b)(4) and for 24 of these batches its value was (b)(4) (reporting limit).

The available stability data drug substance, which includes (b)(4) storage at long-term conditions (25 °C/60 % RH) and also at 30 °C/65 % RH and 5 °C, 6 months at accelerated conditions (40 °C/ 75 % RH), and diverse stress conditions, showed that the drug substance is a stable compound under these conditions. The proposed re-test period (b)(4) under the recommended storage condition, (b)(4) is fully supported by the stability data.

Waiver granted: Removal of testing for (b)(4) content after successful manufacturing of release of first 10 batches.

- Drug Product

The drug product, (b)(4) (dapagliflozin) Tablets, is formulated as immediate release film-coated tablets. Two dose strengths are proposed for marketing, 5 and 10 mg, to be supplied in 95-cc (30-count) and 200-cc (90-count) HDPE bottles (b)(4) and in (b)(4) blister (b)(4). The formulations contain dapagliflozin (active moiety), anhydrous lactose (b)(4) microcrystalline cellulose (b)(4) silicon dioxide (b)(4), crospovidone (b)(4), magnesium stearate (b)(4). All excipients, including the components of the coating agent, meet compendial requirements. The two strengths are differentiated by debossed markings, shape and size.

The Applicant used Quality by Design (QbD) approach to develop the proposed drug product manufacturing process. Quality target product profile (QTPP) is defined. The manufacturing process uses a (b)(4) process (b)(4)

The Firm has proposed a maximum batch size (b)(4) for the commercial manufacturing operation. The proposed manufacturing process consists of (b)(4) operation (b)(4)

The Applicant has completed a manufacturing process risk assessment using Failure Mode and Effect Analysis (FMEA) and assigned a high Risk priority number (RPN) (b)(4)

These steps are considered critical steps as they are linked to the following quality attributes: assay, content uniformity, appearance, dissolution and disintegration and the Firm has proposed limits for these critical process parameters.

The Applicant used experimental design approach (DOE) to establish a design space for the commercial process. The design space includes ranges for the process parameters and process attributed used to control respective unit operation.

Drug product specifications include appearance or description (visual examination), identification (IR and HPLC), assay (HPLC), impurities (HPLC), disintegration as surrogate of dissolution, content uniformity (b) (4). Regarding impurities, acceptance criteria requires (b) (4).

All drug product critical attributes identified by risk assessment and developmental studies are part of the specifications.

The Applicant has performed a total of nine commercial scale batches (b) (4) to demonstrate the transferability of the manufacturing process.

Six batches (three 5 mg and three 10 mg strength batches) have been manufactured to conduct the primary stability study. The stability program consists of long term testing at 25 °C/60 % RH and 30 °C/65 % RH, accelerated testing at 40 °C/75 % RH. The stability protocol includes matrix testing design. The long term stability is still ongoing, but data from the first 24 months are available and show that little or no change was observed for samples packaged in HDPE bottles or (b) (4) blisters (proposed commercial packaging). The 6 month study under accelerated conditions has been completed and their results show that the drug product is stable when stored in HDPE bottles or (b) (4) blisters at 40 °C/75 % RH for up to six months. The requested expiry dating of 24 months for the drug product packaged into HDPE bottles (b) (4) or into (b) (4) blisters at the recommended storage condition: "Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86 °F), is fully supported by the provided stability data. (b) (4)

Waivers granted: (1) Disintegration testing as a surrogate for dissolution testing for release and shelf-life, and (2) No impurities/degradants testing for batch release.

B. Description of How the Drug Product is Intended to be Used

(b) (4) Tablets are film-coated tablets designed for immediate release of dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor. (b) (4) (dapagliflozin) Tablets, available in 10 mg, are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended dose (b) (4) is 10 mg taken once daily at anytime of the day regardless of meals. The efficacy (b) (4) is dependent on renal function. (b) (4) should not be used in patients with moderate to severe renal impairment or for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf life. Quality by design (QbD) concepts have been used during development of both drug substance and drug product manufacture. All Applicant's requests, listed below, are deemed acceptable:

Drug Substance:

- Removal of testing for (b) (4) content after successful manufacturing of release of first 10 batches.

Dug Product:

- Disintegration testing as a surrogate for dissolution testing for release and shelf-life
- No impurities/degradants testing for batch release.

III. Administrative

A. Reviewer's Signature

Muthukumar Ramaswamy PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 31-Oct -2011

Xavier Ysem, PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 31-Oct-2011

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief, ONDQA/ DNDQA III/ Branch VII Date: 31-Oct-2011

C. CC Block

Mehreen Hai Project Manager, OND/ ODE II/ DMEP

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/s/

XAVIER J YSERN
10/31/2011

ALI H AL HAKIM
10/31/2011

NDA 202-293

 ^{(b) (4)} **(dapagliflozin) Tablets**
5 and 10 mg

Bristol-Myers Squibb (BMS) Company

Muthukumar Ramaswamy PhD

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

(Clinical Review Division: DMEP)

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Chemistry Review Data Sheet

- 1. NDA: 202-293
- 2. REVIEW #: 1
- 3. REVIEW DATE: 24-Aug-2011
- 4. REVIEWER(s): Muthukumar Ramaswamy, PhD, and Xavier Ysern, PhD
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

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6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed Document Date

Original	27-Dec-2011
Amendment(s):	
0040	17-Aug-2011 (updated drug product specifications)
0034	24-Jun-2011 (response to information request on 15-Jun-2011)
0022	20-May-2011 (Stability Data Batches manufactured at the commercial site, Humacao, PR)
0008	23-Mar-2011 (Response to 4-Mar-2011 Filing Letter)
0005	31-Jan-2011 (Proprietary name and alternate proprietary name)
0002	05-Jan-2011 (Establishment and patent information)

7. NAME & ADDRESS OF APPLICANT:

Name: Bristol-Myers Squibb (BMS) Company
 Address: 5 Research Parkway
 Wallingford, CT 06492-7660
 Representative: Amy A. Jennings, Ph.D.
 Director, US /Global Regulatory Lead-Dapagliflozin
 Bristol-Myers Squibb Company
 Telephone: 203-677-3821 [fax 203-677-7435 email amy.jennings@bms.com]

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4) is selected by Astra Zeneca and Bristol-Myers Squibb as the primary candidate for the proprietary name, (b) (4) selected as the secondary candidate (31-Jan-2011)
 Division of Medication Error Prevention and Analysis (DMEPA) does not have objection to proposed proprietary name (b) (4) (04-Apr-2011)
- b) Non-Proprietary Name (USAN): Dapagliflozin
- c) Code Name: BMS-512148
- d) Chem. Type/Submission Priority:
 - Chem. Type: 4 (new combination)
 - Submission Priority: S (substantially equivalent)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Dapagliflozin is an orally active sodium glucose co-transporter 2 (SGLT-2) inhibitor, proposed for the treatment of type 2 diabetes mellitus.
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 5- and 10-mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

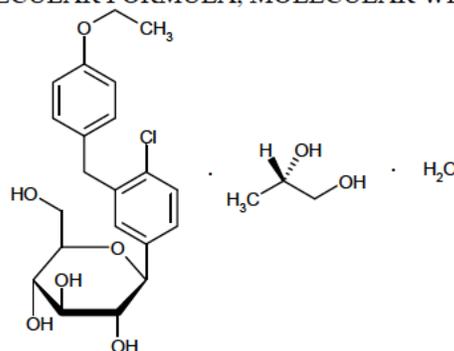
Dapagliflozin propanediol monohydrate

$C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$

MW: 502.98 (Dapagliflozin propanediol monohydrate)
408.87 (Dapagliflozin)

CAS registry #: 960404-48-2

Laboratory Code: BMS-512148-05



D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1)

(2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol,(2S)-propane-1,2-diol (1:1) monohydrate (IUPAC Name)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code ¹	Status ²	LOA date	Comments
Type III		(b) (4)	4	Adequate	10-Aug-2010	DMF (b) (4) pp 1-52
			4	Adequate	12-Jan-2010	21 CFR§314.420
			4	Adequate	29-Jun-2010	(b) (4)
			4	Adequate	09-Sep-2010	21 CFR§210&211
Type IV		(b) (4)	4	Adequate	11-Nov-2010	DMF (b) (4) page 6399 Filed 16-Nov-2009

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68,652	BMS' Dapagliflozin (b) (4)

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Pending (request for Evaluation dated 31-Jan-2011 by Don Henry)		
Pharm/Tox	--		
Biopharm	Approval	27-May-2011	Dr. Minerva Hughes
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
DMEPA	No objection to the proposed Proprietary tradename (b) (4)	04-Apr-2011	
Methods Validation	Revalidation by Agency laboratories is not recommended		
OPDRA			
EA	Acceptable		Part of this review
Microbiology	See Microbiology Review		Dr. Steve Fang

DMEPA = Division of Medication Error Prevention and Analysis.

The Chemistry Review for NDA 22-107

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From CMC point of view this application is recommended for APPROVAL. The recommendation from the Office is Compliance for the acceptability of the manufacturing sites is still outstanding; the CMC recommendation does not incorporate any potential facility inspection issues.

Based on the stability data submitted, an expiry of 24 months for drug product packaged in either HDPE bottles (b) (4) or packaged in (b) (4) blisters is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

- Drug substance

The drug substance (DS), dapagliflozin propanediol monohydrate, is a (b) (4) 1:1:1 mixture of dapagliflozin, propanediol and water (designated as BMS-512148-05). Its chemical name is D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1), empirical formula $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$, and molecular weight 502.98 g/mol (Dapagliflozin 408.87). The active component, dapagliflozin, is a potent, highly selective and orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption, leading to urinary glucose excretion (glucuresis). The mode of action is independent of the presence of insulin.

Dapagliflozin propanediol monohydrate is a (b) (4) compound. Dapagliflozin According to the Biopharmaceutics Classification System (BCS) the drug substance is a class 3 compound (low permeability, high solubility). (b) (4)

The DS will be manufactured at the BMS facility in Swords, Ireland (b) (4)

The Applicant has used quality by design principles to develop the drug substance manufacturing process. Risk assessment techniques were used to assess the influence of process parameters to impact the quality attributes of the intermediates and critical quality attributes of the drug substance. There are no critical process parameters associated with the drug substance manufacturing process. The applicant has identified and defined control ranges for key process parameters (proven acceptable ranges). In addition, the application contains adequate specification for raw materials, intermediates and final drug substance.

Drug substance specifications include appearance, color, identification (IR or Raman, and HPLC), assay (dapagliflozin content by HPLC), (b)(4) content, water content, residual solvents (b)(4) purity (b)(4)

All these specifications were identified by the Applicant as critical quality attributes established for the drug substance linked to patient safety. (b)(4)

Available release data from 30 batches showed that the highest value observed (b)(4) is (b)(4) and for 24 of these batches its value was (b)(4) (reporting limit).

The available stability data drug substance, which includes (b)(4) storage at long-term conditions (25 °C/60 % RH) and also at 30 °C/65 % RH and 5 °C, 6 months at accelerated conditions (40 °C/ 75 % RH), and diverse stress conditions, showed that the drug substance is a stable compound under these conditions. The proposed re-test period (b)(4) under the recommended storage condition, (b)(4) is fully supported by the stability data.

Waiver granted: Removal of testing for (b)(4) content after successful manufacturing of release of first 10 batches.

- Drug Product

The drug product, (b)(4) (dapagliflozin) Tablets, is formulated as immediate release film-coated tablets. Two dose strengths are proposed for marketing, 5 and 10 mg, to be supplied in 95-cc (30-count) and 200-cc (90-count) HDPE bottles (b)(4) and in (b)(4) blister. (b)(4)

The formulations contain dapagliflozin (active moiety), anhydrous lactose (b)(4), microcrystalline cellulose (b)(4), silicon dioxide (b)(4), crospovidone (b)(4), magnesium stearate (b)(4). All excipients, including the components of the coating agent, meet compendial requirements. The two strengths are differentiated by debossed markings, shape and size.

The Applicant used Quality by Design (QbD) approach to develop the proposed drug product manufacturing process. Quality target product profile (QTPP) is defined. The manufacturing process uses a (b)(4) process (b)(4)

The Firm has proposed a maximum batch size (b)(4) for the commercial manufacturing operation. The proposed manufacturing process consists of (b)(4) operation (b)(4)

The Applicant has completed a manufacturing process risk assessment using Failure Mode and Effect Analysis (FMEA) and assigned a high Risk priority number (RPN) (b)(4)

These steps are considered critical steps as they are linked to the following quality attributes: assay, content uniformity, appearance, dissolution and disintegration and the Firm has proposed limits for these critical process parameters.

The Applicant used experimental design approach (DOE) to establish a design space for the commercial process. The design space includes ranges for the process parameters and process attributed used to control respective unit operation.

Drug product specifications include appearance or description (visual examination), identification (IR and HPLC), assay (HPLC), impurities (HPLC), disintegration as surrogate of dissolution, content uniformity (b) (4). Regarding impurities, acceptance criteria requires (b) (4).

All drug product critical attributes identified by risk assessment and developmental studies are part of the specifications.

The Applicant has performed a total of nine commercial scale batches (b) (4) to demonstrate the transferability of the manufacturing process.

Six batches (three 5 mg and three 10 mg strength batches) have been manufactured to conduct the primary stability study. The stability program consists of long term testing at 25 °C/60 % RH and 30 °C/65 % RH, accelerated testing at 40 °C/75 % RH. The stability protocol includes matrix testing design. The long term stability is still ongoing, but data from the first 24 months are available and show that little or no change was observed for samples packaged in HDPE bottles or (b) (4) blisters (proposed commercial packaging). The 6 month study under accelerated conditions has been completed and their results show that the drug product is stable when stored in HDPE bottles or (b) (4) blisters at 40 °C/75 % RH for up to six months. The requested expiry dating of 24 months for the drug product packaged into HDPE bottles (b) (4) or into (b) (4) blisters at the recommended storage condition: "Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86 °F), is fully supported by the provided stability data. (b) (4)

Waivers granted: (1) Disintegration testing as a surrogate for dissolution testing for release and shelf-life, and (2) No impurities/degradants testing for batch release.

B. Description of How the Drug Product is Intended to be Used

(b) (4) Tablets are film-coated tablets designed for immediate release of dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor. (b) (4) (dapagliflozin) Tablets, available in 10 mg, are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended dose (b) (4) is 10 mg taken once daily at anytime of the day regardless of meals. The efficacy of (b) (4) is dependent on renal function. (b) (4) should not be used in patients with moderate to severe renal impairment or for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf life. Quality by design (QbD) concepts have been used during development of both drug substance and drug product manufacture. All Applicant's requests, listed below, are deemed acceptable:

Drug Substance:

- Removal of testing for (b) (4) content after successful manufacturing of release of first 10 batches.

Dug Product:

- Disintegration testing as a surrogate for dissolution testing for release and shelf-life
- No impurities/degradants testing for batch release.

III. Administrative

A. Reviewer's Signature

Muthukumar Ramaswamy PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 24-Jul-2011

Xavier Ysem, PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 24-Jul-2011

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief, ONDQA/ DNDQA III/ Branch VII Date: 24-Jul-2011

C. CC Block

Mehreen Hai Project Manager, OND/ ODE II/ DMEP

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/s/

XAVIER J YSERN
08/29/2011

ERIC P DUFFY
09/02/2011

DATE: April 17, 2011

TO: Dapagliflozin Film-Coated Tablets Review Team (NDA 202293)

FROM: Muthukumar Ramaswamy, Ph.D. (Muthukumar.Ramaswamy@fda.hhs.gov, 301-796-1676)

THROUGH: Christine Moore, Ph.D.

SUBJECT: Chemistry Manufacturing Control Considerations for Manufacturing and Product Quality

The purpose of this memo is to outline the manufacturing process for 5 and 10 mg strength dapagliflozin Film-Coated Tablets and to discuss the risk control strategy proposed in the NDA 220293. This memo is not intended to be used as inspectional instructions.

This NDA was submitted by Bristol-Myers Squibb (BMS) Company in support of the drug product proposed for the treatment of Type II Diabetes Mellitus (T2DM). The drug product contains dapagliflozin (active moiety), anhydrous lactose (b)(4), microcrystalline cellulose (b)(4), silicon dioxide (b)(4), crospovidone (b)(4), magnesium stearate (b)(4).

Bristol-Myers Squibb (BMS) Company plans to manufacture the proposed product at the BMS manufacturing sites located at Humacao, Puerto Rico and Mount Vernon, Indiana. The tablets will be packaged at the BMS site located at Mount Vernon, Indiana.

The Firm used Quality by Design (QbD) approach to develop the proposed drug product manufacturing process (Refer to Attachment 1 and 2 for Process Flow and description). The manufacturing process uses a (b)(4) process (b)(4). The Firm has proposed a maximum batch size (b)(4) for the commercial manufacturing operation. The proposed manufacturing process consists of the following unit operations:

(b)(4)

Based on risk assessment and developmental studies the Firm has identified critical quality attributes for the commercial dapagliflozin film-coated tablets as appearance, identity, assay, content uniformity, impurities/degradants, disintegration (b)(4). Assay and content uniformity are considered as critical attributes as it relates to safety and efficacy of the proposed drug. Disintegration is proposed as a surrogate test for dissolution.

The firm has completed a manufacturing process risk assessment using Failure Mode and Effect Analysis (FMEA) and assigned a high Risk priority number (RPN) (b)(4) (Attachment 1, Table 3.2.P.2.3.T03). As a risk mitigation strategy, the Firm has introduced a (b)(4) step (b)(4) (Attachment 1, Figure. 3.2. P.2.3 F06).

The Firm used experimental design approach (DOE) to establish a design space for the commercial process. The design space includes ranges for the process parameters and process attributes used to monitor the respective unit operation associated with the proposed manufacturing process (Refer to Attachment 3, Table 3.2.P.2.3.1.T01).

The Firm has identified [REDACTED] (b) (4) steps as critical steps. [REDACTED] (b) (4)

[REDACTED] These steps are considered critical as they are linked to the following quality attributes: assay, content uniformity, appearance, dissolution and disintegration and the Firm has proposed limits for these critical process parameters (Refer to Attachment 3, Table 3.2.P.3.4.T01, reproduced from the NDA).

[REDACTED] (b) (4)

The Firm has identified the following risk factors during development and technology transfer phase and implemented risk reduction strategies:

[REDACTED] (b) (4)

Based on initial review, it is inferred that the Firm has proposed acceptable risk control strategy for the proposed process.

Reviewer's assessment of risk:

Although the Firm has considered [REDACTED] (b) (4) and also understood [REDACTED] (b) (4)

[REDACTED] the review team would like to highlight the following areas for consideration of the team on pre-approval inspection:

1. **Assessment of manufacturing controls** [REDACTED] (b) (4)

[REDACTED]

2. *The NDA does not contain a master batch record. Therefore, please verify the master batch record for its conformance with the process parameter ranges identified from Design Space (Attachment 3). Where applicable, such verification may include the following:*
 - a. *How action and alert limits are set and how deviations to such limits are corrected.*
 - b. [REDACTED] (b) (4)
 - c. [REDACTED] (b) (4)
3. *Evaluation of hold time procedures* [REDACTED] (b) (4)
4. *Firm's Quality System especially in the area of whether the firm's procedures are consistent with movement within the design space.*
5. *Firm's control procedures* [REDACTED] (b) (4)

Additionally, the firm has used disintegration as a key response factor for defining the target product formulation and process characteristics, but little information was included in the application. The reviewer would appreciate if the investigator could review the operating procedures for disintegration testing to assure that suitable method qualification studies were performed (i.e., equipment, medium, and use of disks).

The CMC reviewer is willing to share their knowledge with the investigator prior to and during the inspection. If you have any questions, please email or call the CMC reviewers Minerva Hughes, Ph.D. (regarding disintegration test. minerva.hughes@fda.hhs.gov; 301-796-7525) and Muthukumar Ramaswamy, Ph.D. (Muthukumar.Ramaswamy@fda.hhs.gov 301-796-1676).

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/s/

MUTHUKUMAR RAMASWAMY
04/27/2011

ALI H AL HAKIM
04/27/2011

ONDQA
IQA (Initial Quality/CMC Assessment)

Division of Metabolism and Endocrinology Products

NDA: 202293

Applicant: Bristol-Myers Squibb

Stamp Date: 28-DEC-2010

PDUFA Date: 28-OCT-2011

Proposed Proprietary Name: [none indicated]

Established Name: Dapagliflozin

Dosage form and strength: Tablet: immediate release
5 mg and 10 mg (anhydrous free base)

Route of Administration: oral

Indications: Type 2 diabetes

CMC Lead: Su (Suong) Tran, ONDQA

ONDQA Fileability: Yes

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CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	The ONDQA Biopharmaceutics Review Staff will review all dissolution-related information and any biowaiver request.
CDRH or CBER	<i>Not Applicable</i>
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
EES	EER was sent to Compliance on 05-JAN-2011 by ONDQA PM.
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Review of Microbial Limits (issue discussed by Microbiology at the Pre-NDA phase)
Pharm/Tox	Evaluation of the genotoxicity potential of identified impurities and degradants.
Quality by Design	The application includes QbD elements (the ONDQA IO was notified on 04-JAN-2011).

This is an electronic NDA, filed as a 505(b)(1) application. The supporting IND is IND 68652.

The drug substance dapagliflozin propanediol monohydrate is a New Molecular Entity (NME) and a small synthetic compound. It is an inhibitor of the sodium glucose co-transporter 2.

The drug product is an immediate release tablet, 5 mg and 10 mg (anhydrous free-base) containing these excipients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. The film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

The product will be packaged in bottles (b) (4) and (b) (4) blisters, and will be stored at room temperature.

Maximum daily dose is 10 mg dapagliflozin (anhydrous free-base).

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
 Yes. See the summary in 2.3.Quality Overall Summary – Introduction.

The tabulated QTPP and CQAs are copied on the next pages.

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Table 2.3.P.2.T01: Quality Target Product Profile for Dapagliflozin Tablets

QTPP Element	Target	
Dosage form	Film-coated tablet	
Route of administration	Oral, once daily	
Dosage strengths	(b) (4) 5-mg, and 10-mg unit doses	
Container closure system	HDPE bottles (b) (4) blister packs	
Dissolution /pharmacokinetic profile requirements	(b) (4)	
Drug product quality criteria: Appearance	(b) (4)	
Identity		
Assay (potency)		
Content uniformity		
Impurities/Degradants		
Dissolution		
Disintegration		
Microbial quality		
Patient population targeted		Adults
Climate zones targeted for distribution and shelf-life		(b) (4)
Administration	Tablets suitable for self administration by patient as well as nurse/physician in a health care facility or primary care givers at home	

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Table 2.3.P.2.T02: Critical Quality Attributes of Dapagliflozin Film-Coated Tablets

Critical Quality Attribute	QTTP Element Impacted	Rationale
Appearance	Appearance	The appearance of the tablets must be acceptable such that the patient will comply with the dosing regime.
Identity	Identity	The drug substance must be of the required chemical structure in order to deliver the desired efficacy and safety profile.
Assay	Assay (potency)	Assay is related to dose delivered to patient; thus, for safety and efficacy, needs to comply with the limits established for drug content.
Content uniformity	Content uniformity	Content uniformity is related to consistency of dose delivered to the patient; thus, for efficacy and safety, needs to comply with harmonized acceptance criteria for uniformity of dosage units.
Disintegration	Disintegration Dissolution	Disintegration is used as a surrogate test for dissolution. Disintegration needs to be rapid to make certain that dapagliflozin is available for dissolution.
(b) (4)		
(b) (4)		

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Drug substance:

Generic Name (INN, USAN): Dapagliflozin propanediol

Chemical Names:

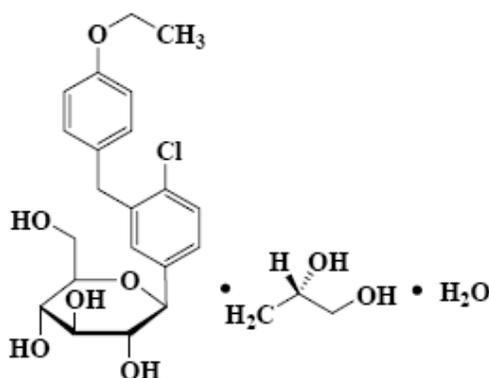
CA Index Name D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compd. with (2S)-1,2-propanediol, hydrate (1:1:1)

IUPAC Name (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, (2S)-propane-1,2-diol (1:1) monohydrate

Laboratory Code: BMS-512148-05

CAS Registry Number: 960404-48-2

Chemical Structure:



Molecular Formula: C₂₁H₂₅ClO₆ • C₃H₈O₂ • H₂O

Formula Weight: 502.98

Molecular Weight: 408.87 (dapagliflozin)

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ONDQA
 IQA (Initial Quality/CMC Assessment)

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 202293

Applicant: BMS

Letter Date: 28-DEC-2010

Established/Proper Name:

Dapagliflozin

Stamp Date: 28-DEC-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

ONDQA
 IQA (Initial Quality/CMC Assessment)

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

ONDQA
 IQA (Initial Quality/CMC Assessment)

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?			See Biopharm filing memo
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		Review issue: whether data and analysis are adequate to support expiry
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	x		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Non-sterile solid oral dosage form.
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		Submit no later than 6 months after the initial NDA submission all available stability data for the drug product batches manufactured at the commercial Curacao site; these batches are listed in Table 3.2.P.5.4.T01.

{See appended electronic signature page}

Su (Suong) Tran

CMC Lead, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim

Branch Chief, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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/s/

SUONG T TRAN
02/14/2011

ALI H AL HAKIM
02/14/2011